Original Article

Comparison of Biodegradable Polymer Biolimus A9 Eluting Stents versus Durable Biocompatible Polymer Everolimus Eluting Stents in the Treatment of Coronary Bifurcation Lesions

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Objective: To compare the long-term clinical outcomes between biodegradable polymer-coated biolimus A9-eluting stent [BES] and durable biocompatible polymer-coated everolimus-eluting stent [EES] in the treatment of bifurcation lesions according to Thailand's universal coverage scheme.

Materials and Methods: The authors retrospective reviewed bifurcation lesions treated either with BES or EES in their institution between January 2010 and December 2015. The incidence of target vessel failure [TVF] (a composite of cardiac death, myocardial infarction [MI], and target vessel revascularization [TVR]) in five years were compared between the two groups.

Results: One hundred sixty bifurcation lesions treated with BES in 84 lesions and EES in 76 lesions were analyzed. Patient and procedural characteristics were comparable between the two groups. One stent strategy was performed in similar proportion between the two platforms (BES 81% versus EES 75%, $p = 0.44$). There were no statistically significant differences in TVF rates between the two groups (BES 11.9% versus EES 14.5%, $p = 0.75$). The incidence of TVR (BES 6.0% versus EES 3.9%, $p = 0.72$) and stent thrombosis [ST] (BES 1.2% versus EES 1.3%, $p = 1.00$) were comparable between the two groups.

Conclusion: The long-term clinical outcomes in the treatment of coronary bifurcation lesions under Thailand's universal coverage scheme was comparable between BES and EES. There was a comparable rate of ST irrespective of the types of polymer.

Keywords: Biolimus-eluting stent, Everolimus-eluting stent, Coronary bifurcation

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Coronary bifurcation lesions are common and attributed to 20% of all percutaneous coronary interventions [PCI][1-4]. Owing to the complexity of the disease, patient with true bifurcation lesions had more major adverse cardiac events than those with non-bifurcation lesions[5]. To improve the treatment outcomes in bifurcations, intensive research have focused on the treatment strategies between single stent strategy or two-stent strategies. Currently, the provisional side branch [SB] stenting with proximal optimization technique [POT] is a preferred approach[6,7] whereas the two-stent strategies should be considered upfront when (i) the SB is diseased and large enough, leading to significant ischemia, and (ii) future access toward the SB may be important[8].

Along with the refinement of bifurcation PCI techniques, the stent technology has been improved to meet the favorable device performance. One innovation is the introduction of biodegradable polymer. The alteration from durable to biodegradable polymer is anticipated to reduce the complication related to hypersensitivity reaction from the permanent polymer such as delayed endothelialization and late-acquired malapposition leading to late stent thrombosis [ST][9,10].

According to the Thailand's universal coverage scheme, the frequently used stent platforms consisted of (i) the abluminal biodegradable polymer-coated biolimus A9-eluting stent [BES] (BioMatrix™ or BioMatrixFlex™, Biosensors, Switzerland), and (ii) the durable biocompatible polymer-coated everolimus-eluting stent [EES] (Xience V™ or Xience Prime™,

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Abbott, USA). The current study aimed to compare the long-term clinical outcome between the two stent platforms, which have been widely used in Thailand according to the universal coverage program.

Materials and Methods

Study population

The present study was a retrospective reviewed of medical record to identify patients treated with PCI between January 2010 and December 2015. The study flow chart is shown in Figure 1. The inclusion criteria were age more than 18 years old and presented with bifurcation lesions required revascularization. Bifurcation lesion was defined as a coronary artery narrowing occurring adjacent to, and/or involving the origin of a significant SB. A significant SB is a branch whose loss is of consequence to particular symptoms, location of ischemia, viability of the supplied myocardium, collateralizing vessel, left ventricular function[11]. Key exclusion criteria were evidence of ongoing acute ST-segment elevation myocardial infarction [STEMI] prior to the procedure, pregnancy, known hypersensitivity or contraindication to aspirin, clopidogrel, heparin, stainless steel, cobalt-chromium, biolimus, everolimus, or contrast material. The informed consent was obtained from every patient before any intervention was performed. The present study protocol was approved by the Institutional Ethical Committee. Patients with bifurcation lesions (including left main lesion) that successfully treated with BES or EES implantation at main branch were identified from the electronic case report form. The lesions severity was assessed by visual estimation by the investigators using the Medina score. The Medina score indicates for each of the three bifurcation segments separately whether a 50% or greater stenosis is present (as '1') or absent (as '0') in the following order: proximal main branch-distal main branch-SB, resulting in scores ranging from Medina 0.0.0 to Medina 1.1.1[12]. By using this strategy, 210 patients (110 BES, 100 EES) were identified. The chosen strategy for bifurcation treatment was at the discretion of the operator.

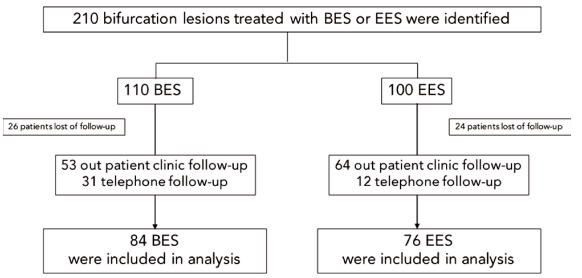


Figure 1. Flow chart of the current study.

Device description

BioMatrix™/BioMatrix Flex™ (Biosensors International, Morges, Switzerland) is a balloon expandable stainless-steel stent. The strut thickness is 120 µm with a biodegradable polymer coating of polylactic acid [PLA] on its abluminal surface. Stent diameter 2.25 to 3.0 mm has six crowns and two connectors whereas stent diameter 3.5 to 4.0 mm has nine crowns and three connectors[13].

Xience V™/Xience Prime™ (Abbott Vascular, Santa Clara, CA, USA) is a balloon expandable stent, manufactured from a flexible cobalt chromium [CoCr] alloy, and coated with a thin non-adhesive, durable, biocompatible acrylic, and fluorinated everolimus-releasing copolymer. The overall strut thickness including the drug coating is approximately 90 µm. Stent diameter 2.25 mm to 3.5 mm has six crowns and three connectors and stent diameter 3.5 to 4.0 mm has nine crowns and three connectors[14].

Study endpoints

Clinical follow-up was performed via medical record by clinic visit or by telephone interview. Measured endpoints were target vessel failure [TVF] defined as the composite of cardiac death, myocardial infarction [MI], and target vessel revascularization [TVR]. Death was considered cardiac in origin unless obvious non-cardiac causes were identified. Spontaneous MI was defined by the third universal definition[15]. TVR was defined as percutaneous revascularization or bypass of the target lesion or any segment of the epicardial coronary artery containing the target lesion or more proximal vessels that may have been traversed by the angioplasty guidewire during the index procedure[16]. ST was defined on the basis of the Academic Research Consortium definition[16].

Statistical analysis

The primary endpoint was the TVF rates. To exclude a different TVF rate of more than 8% between the two groups, a sample size of 301 patients per group was required to achieve 80% power with a 2-tailed significance level of 5%. Due to the nature of single center study, the study could collect only 210 patients during the study period. Continuous variables were presented as means ± standard deviation or medians and interquartile ranges [IQR] as appropriate.

The categorical variables were summarized with frequencies and percentages. Comparison between the two groups was performed using the Chi-square test for categorical variables and the independent t-test or Mann-Whitney U-test for continuous variables. Cumulative event rates were estimated using the Kaplan-Meier method and compared by log-rank test. Statistical significance was considered as a 2-tailed probability of less than 0.05. Analyses were performed by SPSS for Windows, version 19.0 (SPSS Inc., Chicago, Illinois).

Results

Baseline clinical characteristics

Baseline patient characteristics are summarized in Table 1. There were well matched between the two groups. Mean age was 64.1±10.7 and 64.7±11.2 years in BES and EES group, respectively ($p = 0.69$). Most patients in both groups were male (60.7% in BES versus 59.2% in EES, $p = 0.87$). Left ventricular ejection fraction [LVEF] was comparable between the two groups (BES 50.3±14.6% versus EES 53.5±12.3%, $p = 0.26$). There were no significant differences in the presence of cardiovascular risk factors between BES and EES groups.

Lesion and procedural characteristics

Lesion and procedural characteristics are summarized in Table 2. The most common bifurcation lesions were located at left anterior descending [LAD] and diagonal branch in both groups. The proportions of true bifurcation lesions were comparable between the two groups (BES 77.4% versus EES 78.9%, $p = 0.85$). The single stent strategy was the most utilized

Table 1. Baseline patient characteristics

	BES (n = 84)	EES (n = 76)	*p*-value
Age (years)	64.1±10.7	64.7±11.2	0.69
Male	51 (60.7)	45 (59.2)	0.87
Left ventricular ejection fraction (%)	50.3±14.6	53.5±12.3	0.26
Diabetes mellitus	21 (25.3)	24 (37.5)	0.15
Hypertension	56 (67.5)	49 (76.6)	0.27
Hypercholesterolemia	47 (56.6)	44 (64.7)	0.32
Current smoker	10 (12.0)	8 (12.5)	1.00
Prior MI	21 (71.4)	24 (61.3)	0.18
Prior PCI	11 (13.3)	5 (6.7)	0.20
Prior CABG	2 (2.4)	3 (4.1)	0.67
NSTEMI	37 (44.0)	28 (39.4)	0.65
Multivessel diseases	59 (70.2)	61 (80.3)	0.20

BES = biolimus-eluting stent; EES = everolimus-eluting stent; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; NSTEMI = non-ST elevation myocardial infarction

Data are shown in mean ± SD or n (%)

Table 2. Lesion and procedural characteristics

	BES (n = 84)	EES (n = 76)	*p*-value
Bifurcation site			0.54
Left main	14 (16.7)	10 (13.2)	0.66
LAD/diagonal branch	59 (70.2)	55 (72.4)	0.86
LCX/obtuse marginal branch	3 (3.6)	6 (8.0)	0.31
RCA/RPD/PL	8 (9.5)	6 (7.9)	0.78
Medina bifurcation classification			0.77
1.0.0	6 (7.1)	2 (2.6)	
0.1.0	1 (1.2)	2 (2.6)	
1.1.0	13 (15.5)	14 (18.4)	
1.1.1	32 (38.1)	30 (39.5)	
0.0.1	0 (0.0)	0 (0.0)	
1.0.1	6 (7.1)	2 (2.6)	
0.1.1	26 (31.0)	26 (34.2)	
True bifurcation*	65 (77.4)	60 (78.9)	0.85
Bifurcation angle <70 degree	58 (69.0)	52 (69.3)	0.55
Calcified lesions	3 (3.6)	6 (7.9)	0.31
Pre-dilatation, main-branch	81 (96.4)	74 (97.4)	1.0
Pre-dilatation, side branch	40 (47.6)	34 (44.7)	0.75
Main branch stent			
Nominal stent diameter (mm) at maximum pressure	3.19±0.55	3.15±0.48	0.63
Stent length (mm)	39.9±19.3	36.9±15.5	0.30
Maximum balloon pressure (atm)	13.9±3.0	13.5±3.3	0.38
Side branch stent			
Nominal stent diameter (mm) at maximum pressure	2.65±0.31	2.88±0.44	0.08 0.92
Stent length (mm)	18.8±11.4	19.5±9.3	0.33
Maximum balloon pressure (atm)	11.6±2.8	12.5±2.6	
Implantation strategies			
One stent technique	68 (81.0)	57 (75.0)	0.44
Two-stent technique	16 (19.0)	19 (25.0)	0.44
Jailed wire used	53 (63.1)	43 (56.6)	0.42
Two-stent technique			0.17
Crush	2 (12.5)	3 (16.7)	
T-stenting	10 (62.5)	15 (83.3)	
V-stenting	3 (18.8)	0 (0.0)	
Culotte	1 (6.3)	0 (0.0)	
Crossover	6 (7.1)	4 (5.3)	0.75
Final kissing balloon inflation	24 (28.6)	18 (23.7)	0.59
Post-dilatation, main-branch	75 (89.3)	64 (84.2)	0.36
Post-dilatation, side branch	29 (34.5)	25 (33.3)	1.00
Unable to wire side branch	5 (6.0)	2 (2.7)	0.45

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; RPD = right posterior descending; PL = posterolateral branch

Data are shown in mean ± SD or n (%)

Medina classification consisted of 3 segments in the following order: proximal segment, main distal segment, side branch. Each segment is assigned a value 0 in the absence of significant stenosis and 1 in the presence of a stenosis >50%. * True bifurcation includes: 1.1.1; 1.0.1; 0.1.1

in both groups (BES 81.0% versus EES 75.0%, p = 0.44). Among the two-stent strategies, T-stenting was frequently used during the procedure (BES 62.5% versus EES 83.3%, p = 0.17). However, there was a comparable rate of final kissing balloon inflation [FKBI] in both groups (BES 28.6% versus EES 23.7%, p = 0.59). The stent diameter, stent length in main branch and SB were comparable between the two groups (Table 2). During the procedure, the balloons were inflated with low to moderate pressure. The maximum balloon inflation pressure in main branch was 13.9±3.0 atm in BES group and 13.5±3.3 atm in EES group (p = 0.38). The maximum balloon inflation pressure inside branch was 11.6±2.8 atm in BES and 12.5±2.6 atm in EES (p = 0.33).

Clinical outcomes: BES versus EES

Clinical outcomes are summarized in Table 3. The follow-up period was comparable between the two groups (BES 25.5 months [IQR 19.5 to 36.0 months] versus EES 24.0 months [IQR 12.0 to 48.0 months], p = 0.29). There were no statistically significant differences between BES and EES with regard to the TVF rates (BES 11.9% versus 14.5%, p = 0.75) (Figure 2). The 5-year rate of all cause death (BES 7.1% versus EES 9.2%, p = 0.77), cardiac death (BES 2.4% versus EES 5.3%, p = 0.42), MI (BES 6.0% versus EES 7.9%, p = 0.76), and TVR (BES 6.0% versus EES 3.9%, p = 0.72) was comparable between the groups. There was only one ST observed in each group.

Discussion

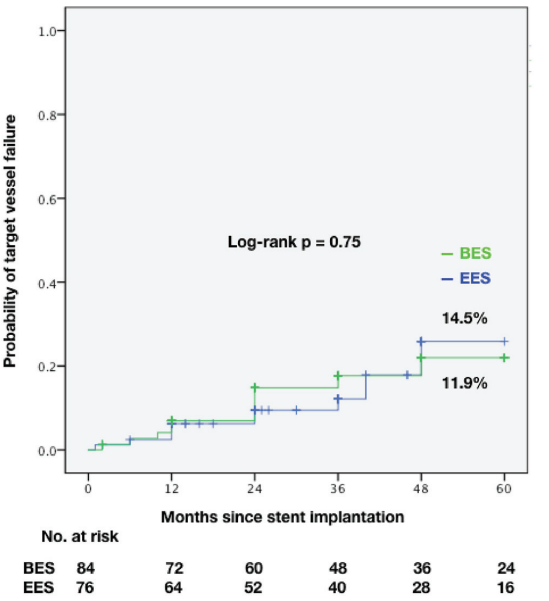
The main finding of the current analysis is that the TVF rate and safety of the biodegradable polymer BES is as equal as the durable biocompatible polymer EES for the treatment of bifurcation lesions.

Table 3. Clinical outcomes

Clinical outcomes	BES (n = 84)	EES (n = 76)	p-value
Follow up period (month)	25.5 (19.5 to 36.0)	24.0 (12.0 to 48.0)	0.29
All-cause death	6 (7.1)	7 (9.2)	0.77
Cardiac death	2 (2.4)	4 (5.3)	0.42
MI	5 (6.0)	6 (7.9)	0.76
TLR	3 (3.6)	2 (2.6)	1.00
TVR	5 (6.0)	3 (3.9)	0.72
Composite of cardiac death, MI, TVR (TVF)	10 (11.9)	11 (14.5)	0.75
Stent thrombosis (definite/probable)	1 (1.2)	1 (1.3)	1.00

BES = biolimus-eluting stent; EES = everolimus-eluting stent; MI = myocardial infarction; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization

Data are shown in median (IQR 1st to 3rd) or n (%)



BES, biolimus-eluting stent; EES, everolimus-eluting stent

Figure 2. Cumulative event rates (Kaplan-Meier estimates) of patients with bifurcation lesion treated with biolimus-eluting stents [BES] and everolimus-eluting stents [EES].

Bifurcation lesion is a complex lesion, owing to the worse clinical outcome than those without bifurcation involvement. Previously, Costopoulos et al reported that MACE and TVR rates at 2-year follow-up in bifurcation lesions were similar between the BES and EES groups. In their study, the MACE rates and TVR rates of BES and EES were 13.6±4.6% and 14.6±3.2% (p = 0.871) and 6.9±3.5% versus 8.0±2.7% (p = 0.889), respectively*(17)*. Compared to the current study, the BES in the earlier study included two BES, BioMatrix™ and Nobori™, on the one hand, the EES arm included two EES, Xience™ and Promus™. The mixing of two stent platforms in each arm precluded individual assessment of stent platform in the treatment of bifurcation.

Some specific stent properties are required to achieve favorable clinical and angiographic results in the treatment of bifurcation lesions. Ideally, it should have large cell opening that ease SB rewiring, dilatable to maximum diameter without loss in radial strength, and conform to the vessel contour. In a previous bench test, BES, BioMatrix Flex™ has revealed some of these theoretical properties[13]. When BES and EES were inflated to the overexpansion status, Biomatrix Flex™

could achieve larger cell opening than Xience V™ (Biomatrix Flex™ 2.0 to 2.4 mm versus Xience V™ 1.7 to 1.8 mm). Nevertheless, the current study showed no significant difference in term of the SBs access between the two groups despite the BES platform had a larger cell opening diameter than the EES. These findings could be explained by the operator's preference during the procedure. The authors' institute rarely used jailed wire technique and POT technique during the procedure, which might impact on the success of SB rewiring more than the inherent cell opening property. The longer follow-up period would be a plausible explanation for a high TVF rates in the current study compared to the previous reports.

Limitation

There were several limitations in the present study that should be acknowledged. First, due to the nature of retrospective study design, the sample size was not powered to definitely establish superiority or non-inferiority between the two platforms. Based on the results of previous bifurcation studies, a sample size of approximately 200 patients would be required to demonstrate non-inferiority of BES as compared to EES with regards to MACE. A prospective randomized trial is required to confirm our findings or further demonstrate a superiority of BES. Second, the use of various bifurcation techniques and the operator's experience may also affect the clinical outcomes. Third, we did not report bifurcation QCA data because the retrospective nature of the present study made it impossible to obtain high quality images for bifurcation analysis. Forth, the lack of angiographic follow-up did not allow us to precisely evaluate the occurrence of in-stent restenosis in each stent platform. Finally, due to the retrospective data collection, we obtained clinical endpoints by reviewing clinical visit from medical record or telephone interview. These strategies would have led to under-reporting of ST event.

Conclusion

The long-term clinical outcomes in the treatment of coronary bifurcation lesions under Thailand's universal coverage scheme was comparable between BES and EES. There was a comparable rate of ST irrespective of the types of polymer coated on the stent.

What is already known on this topic?

According to the design of BES, Biomatrix Flex™, that allows a larger cell opening than the EES, Xience V™, it has been speculated that BES might be associated with favorable clinical outcomes in the treatment of bifurcation lesions.

What this study adds?

The result of this study showed that the implantation strategies impact on the success of SB rewiring more than the inherent cell opening property. There was a low rate of ST irrespective of the types of polymer coated on the stent.

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Potential conflicts of interest

The authors declare no conflict of interest.

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